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(51) International Patent Classification 6
A61K 31/415, 31/14, 31/47

A1

(11) International Disclosure No.: WO 96/40121

(43) Date of International Disclosure: 19 December 1996 (19.12.96)

(21) International Patent Application No.: PCT/JP96/01533
(22) International Application Date: 7 June 1996 (07. 06. 96)

(30) Priority Right Data
Patent Application No. 7/140598, 7 June, 1995 (07. 06. 95) JP

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Appended Disclosure Documents -International Search Report

(54) Title of the Invention: AN ANTIFUNGAL AGENT

(57) Abstract

The composition having antifungal action is characterized in that an imidazole antifungal agent and a quaternary ammonium salt are compounded, in that it is a drug that can further increase the efficacy of miconazole nitrate against both Trichophyton and Candida albicans and that it has a high therapeutic effectiveness.

SPECIFICATION

An Antifungal Agent

Field of Technology

This invention relates to an antifungal agent. In greater detail, it relates to a composition having antifungal action characterized in that an imidazole antifungal agent and a quaternary ammonium salt are compounded.

Background Technology

Imidazole antifungal agents, which are the mainstream antifungal agents in use in the world, are drugs that have an imidazole group in their chemical structure. Their antifungal action is displayed primarily by impairing the cell membrane of the fungus.

The imidazole antifungal agents clotrimazole, miconazole nitrate, econazole nitrate, bifonazole, oxiconazole nitrate and tioconazole are known as switch OTC components.

Clotrimazole is used as a topical agent and is effective against Trichophyton and Candida. When it is used on healthy skin, almost none of it is absorbed in the body. However, its local side effects include a feeling of irritation and redness and exanthema of the skin. It is thought that direct stimulating action and allergic action on the skin are involved.

Bifonazole has an action similar to that of clotrimazole. It is effective against many human pathogenic fungi. It has superior skin penetrating action on topical use by comparison to other imidazole antifungal agents and exhibits a high degree of retention in skin tissues. Local side effects similar to those of clotrimazole include a feeling of irritation and redness and exanthema of the skin.

Miconazole nitrate and econazole nitrate exhibit antifungal activity against Trichophyton, Candida, Aspergillus and Cryptococcus. When they are applied to healthy skin, almost no absorption into the body is found. On ordinary topical use, there are essentially no systemic side effects. However, locally, side effects similar to those of clotrimazole are seen.

The term quaternary ammonium salt refers to cationic surfactants and are substances that belong to the category of quaternary ammonium salts. For example, they include benzethonium chloride, benzalkonium chloride and decalinium* chloride. Cations of quaternary ammonium salts are adsorbed on the surfaces of the fungi, enter the cells and affect the proteins in the cells, by which means they display their fungicidal action.

Benzethonium chloride and benzalkonium chloride exhibit microbicidal action on gram positive bacteria and fungi. When they are applied for long periods to the skin, their side effects include symptoms of hypersensitivity, coarsening of the skin, exanthema and itching.

* Translator's Note: Transliterated phonetically from the Japanese. We have not been able to reference this compound from the various sources available to us.

Decalinium chloride exhibits microbicidal activity against bacteria (especially, Staphylococcus aureus and Streptococcus hemolyticus) and fungi. It is compounded primarily with oral cavity microbicidal agents and with toothache and alveolar blennorrhea agents.

Agents in which imidazole antifungal agents and quaternary ammonium salts are compounded are not known. However, examples of compounding of imidazole antifungal agents with salicylic acid or benzoic acid are presented in British Patent Application Early Disclosure No. 2208598.

Disclosure of the Invention

In general, drugs must be applied for long periods in the treatment of fungal conditions which are said to be difficult to treat and there is a desire for the development of drugs of high therapeutic effectiveness with which the symptoms of fungal conditions can be completely controlled during winter and with which the activity of the fungi is mitigated. Differentiation as to whether the cause of fungal symptoms is Trichophyton or Candida can be made only under the microscope by medical specialists or by culturing of the fungi. Because they are difficult to differentiate, a drug which is effective against both of them is important. Further, as mentioned previously, the local side effects of imidazole antifungal agents include feelings of irritation and redness and exanthema of the skin. It is necessary to decrease the quantity of their compounding in the drug preparation and to eliminate the occurrence of side effects.

With the objective of obtaining a drug having fungicidal activity against both Trichopyton and Candida and of improving use feel, the inventors performed various screenings for the purpose of selecting drugs that act effectively with imidazole antifungal agents. It was discovered that quaternary ammonium salts have a synergic, intensifying effect on microbicidal activity. This invention was perfected on the basis of this finding.

Specifically, this invention is a composition having antifungal action characterized in that imidazole antifungal agents and quaternary ammonium salts are compounded.

Desirable imidazole antifungal agents include miconazole, econazole, clotrimazole and bifomazole. In addition, salts of micaonazole and econazole can also be used. Nitrates are in particularly wide use.

The term quaternary ammonium salt refers to substances belonging to the category of quaternary ammonium salts that are cationic surfactants. Desirable substances for this invention are benzethonium chloride, benzalkonium chloride and decalinium chloride.

The quantity of imidazole antifungal agent compounded is 0.2 to 1 weight %, and, preferably, 0.5 to 1 weight %.

The quantity of quaternary ammonium salt compounded is 0.1 to 1 weight %, and, preferably, 0.5 to 1 weight %. For example, the quantity of benzethonium chloride compounded is 0.5 to 1.0 weight % and the quantity of benzalkonium chloride compounded is 0.1 to 1 weight %, and, preferably, 0.5 to 1 weight %.

The quaternary ammonium salt should be compounded in amounts of 0.1 parts by weight to 1 part by weight, and, preferably, of 0.1 parts by weight to 0.5 parts by weight, per 1 part by weight of imidazole antifungal agent.

The effective component of this invention, as required, can be mixed with known additives and can be made by standard methods into topical preparations such as liquid agents, lotions, emulsions, tinctures, ointments, creams, aqueous gels, oleaginous gels and aerosols.

Examples of water-soluble components include propylene glycol, 1,3-butylene glycol, glycerol, ethanol and macrogols.

Examples of oleaginous components include diisopropyl adipate, stearyl alcohol, cetanol, squalane and neutral chain triglycerides.

Examples of polymers include carboxyvinyl polymers and methyl cellulose.

Examples of pH regulating agents include citric acid, inorganic bases such as sodium hydroxide and organic amines such as diisopropanolamine.

Antioxidants include butyl hydroxy toluene (BHT), butyl hydroxy anisole (BHA), α-tocopherol, erythorbic acid and sodium pyrosulfite.

Titanium oxide is an example of a colorant.

Surfactants can include, for example, polyoxyethylene hardened castor oil, sorbitan monostearate, sorbitan monopalmitate, monostearic acid glyceride, sorbitan monolaurate, polyoxyethylene polyoxypropylene block copolymers, polysorbates, sodium lauryl sulfate, sucrose fatty acid esters and lecithin.

An example of a stabilizer is EDTA-2Na.

A particularly desirable composition of this invention having an antifungal action is one characterized in that an imidazole antifungal agent and decalinium chloride are compounded.

Specifically, when a study was made of skin irritability and preparations involving quaternary ammonium salts found to have a synergic fungicidal effect, decalinium chloride was found to be optimum as shown in Table 1.

Table 1

Name of compound	Suitability as preparation	Skin irritabiliuty
Benzalkonium chloride	O	Δ
Decalimium chloride	O	O

In this invention, the effective compounding quantity of miconazole nitrate is 0.2 to 1 weight %, and, preferably, 0.5 to 1 weight %.

Further, the effective compounding quantity of decalinium chloride is 0.05 to 0.5 weight %, and, preferably, 0.1 to 0.5 weight %.

Decalinium chloride is used in an amount of 0.1 part by weight to 1 part by weight, and, preferably, 0.1 part by weight to 0.5 part by weight, per 1 part by weight of miconazole nitrate.

Possibility of Industrial Use

The drug preparation of this invention is an antifungal agent of extremely strong potency having an intensified fungicidal effect.

We shall now show the effect of this invention in specific terms by presenting experimental examples.

Experimental Example 1

Test fungal strains

The following fungi were used as test fungal strains.

Trichophyton rubrum

Trichophyton mentagrophytes

Method of preparation of spore solution

The test microorganisms were inoculated on the slant of a test tube into which 1/10 Sabouraud agar culture medium was introduced and they were cultured for 3 to 4 weeks at 28°C. After culturing, the microorganisms were scratched off with a sterilized spatula and transferred to an Erlenmeyer flask (100 ml capacity) into which sterilized glass beads and physiological saline solution containing 10 ml of 0.1% Tween 80 had been introduced. The flask was agitated for 1 hour, after which filtration was performed with a cotton plug and a spore solution was obtained. The spore solution was stored under refrigeration and was used within 1 month.

(Composition of 1/10 Sabouraud agar culture medium)

4.0 g of glucose, 1.0 g of peptone, 1.5 g of potassium dihydrogenphosphate (anhydrous), 1.0 g of magnesium sulfate (7 hydrate), 1.0 g of sodium nitrate, 20.0 g of agar and 1000 ml of distilled water.

Preparation of test drug preparations

The test drug preparations were prepared using miconazole nitrate, benzalkonium chloride, decalinium chloride, benzethonium chloride and salicylic acid. DMSO was used as the solvent for dissolution and dilution and a double dilution series in accordance with the test concentrations was prepared.

(4) Experimental method

The diluted test drug preparation and Sabouraud agar culture medium (Eiken) were mixed at a proportion of 1 : 99 and solidified, after which a spore solution of approximately 10^5 spores/ml was inoculated. They were cultured for 5 days at 28°C and presence or absence of growth of fungi was ascertained.

The DMSO concentration was set to less than 1% so as not to affect germination of the spores.

(5) Evaluation and calculation equation

For evaluation of synergic effect, the fractional inhibitory concentration index (FIC Index) was calculated from the minimum drug preparation concentration and the preparation in which no growth of microorganisms occurred at the time culturing was determined (MIC: minimum growth inhibitory concentration, μg/ml).

(Calculation equation) FIC Index = $a/a_0 + b/b_0$

a : MIC of miconazole nitrate when miconazole nitrate was used in combination with the test drug preparation

MIC of miconazole nitrate alone

b MIC of the test drug preparation when miconazole nitrate and the test drug preparations were used in combination

MIC of test drug preparation alone

(Evaluation) Presence of absence of effect on combined used was evaluated on the basis of the following criteria.

> 2	: antagonist action
Less than 2 to greater than 1	: additive action
Less than	: synergic action

(6) Results

The FIC index value for a judgment of synergic effect was set at less than 1.0 taking into consideration the findings of bacteriostatic evaluations and primary screening.

As a result, as shown in Table 2, additive or synergic effects were found for almost all of the drug preparations.

Table 2

Name of compound	FIC index	
	T. rubrum	T. mentagrophytes
Benzethonium chloride	0.49	0.55
Benzalkonium chloride	0.12	0.26
Decalinium chloride	0.47	0.68
Salicylic acid	0.44	0.72

Experimental Example 2

The following fungi were used as test fungal strains.

Test fungal strains

Trichophyton rubrum

Trichophyton mentagrophytes

Method of preparation of spore solution

It was prepared in the same way as in Experimental Example 1

Preparation of test drug preparations

The test drug preparations were prepared using miconazole nitrate, econazole nitrate, clotrimazole, befonazole and decalinium chloride. DMSO was used as the solvent for dissolution and dilution and a double dilution series in accordance with the test concentrations was prepared.

Experimental method

It was performed in he same way as in Experimental Example 1

Evaluation and calculation equation

Calculations and evaluations were made in the same way as in Experimental Example 1

Results

The results are shown in Table 3

Table 3. Synergic Effects of Imidazole Antifungal Agents and Decalinium Chloride

Name of compound	FIC index	
	T. rubrum	T. mentagrophytes
Miconazole nitrate	0.32	0.53
Econazole nitrate	0.63	1.00
Clotrimazole	0.38	1.25
Nifonazole	0.25	0.14

As shown in Table 3, strong synergic effects were shown with decalinium chloride except for the effect of clotrimazole against T. mentagrophytes.

From the foregoing results, it is evident that synergic effects due to combinations with decalinium chloride were manifested not only with miconazole nitrate but also with all of the imidazole antifungal agents.

Experimental Example 3

(1) Test fungal strains

Trichophyton rubrum

Trichophyton mentagrophytes

(2) Method of preparation of spore solution

It was prepared in the same way as in Experimental Example

(3) Preparation of test drug preparations

The test drug preparations were prepared using miconazole nitrate MCZ, salicylic acid, benzalkonium chloride (BAC) and decalinium chloride (DQ). DMSO was used as the solvent for dissolution and dilution and a double dilution series in accordance with the test concentrations was prepared.

(4) Experimental method

Amounts of 100 µl of the various drug preparations were added to and mixed with amounts of 20 ml of 20 mM phosphate buffer solution that had been filtered and sterilized, after which the spore solution was added (ordinarily 50 to 200 µl) to give 10^5 spores/ml and the mixtures were stirred. The temperature was maintained at 30°C and the numbers of surviving spores on the 1st, 2nd and 3rd days were determined. The DMSO concentration was set to less than 1% so as not to affect germination of spores.

(5) Method of determination of number of surviving spores

For determination of the number of surviving spores in the spore solution and the test solution, a dilutions series at a factor of 10 was prepared using sterilized physiological saline solution and LP diluting solution (Daigo) , 50 µl of each dilute solution was applied to Sabouraud agar culture medium (Eiken) that had been prepared in advance and the numbers of surviving spores in the spore solution and the test solution were calculated on the basis of the number of colonies that appeared on culturing at 28°C when T. rubrum was cultured for 4 days or longer and T. mentagrophytes was cultured for 3 days or longer.

Evaluation of synergic effect

On the basis of the literature (Antimicrobial Agents and Chemotherapy, Feb. 1977, p. 225-228), it was determined that there was a synergic effect when the difference in the number of surviving spores alone and in combination was greater than an order of approximately 2.

[Experimental Results]

Fungicidal curve of miconazole nitrate

The fungicidal activity of miconazole nitrate alone was confirmed in sterilized physiological saline solution (pH 6.5). As a result, as shown in Figure 1, its fungicidal activity increased in a concentration-dependent pattern. For the experiments on the effects of combined use, a concentration of 3.13 μg/ml at which evaluation of synergic fungicidal effect is easily done was selected.

Fungicidal curve on combined use of preparations

Table 4 shows the internal standard maximum compounding ratios with miconazole nitrate of each drug preparation.

Table 4

Name of compound	Compounding ratio*
Salicylic acid	10
Benzalkonium chloride	1
Decalinium chloride	0.5

*) In which the compounding quantity of miconazole nitrate is taken as 1

Fungicidal activity on combined use was confirmed by adding each drug preparation to 3.13 μg/ml of miconazole nitrate at each maximum compounding ratio.

As shown in Figure 2, it was confirmed that fungicidal activity on combined use was greater than when miconazole nitrate was used alone, with the exception of salicylic acid.

Next, detailed studies were conducted of the effects of each drug preparation.

The results for salicylic acid are shown in Figure 3

With salicylic acid alone, no fungicidal activity whatsoever was found. Its fungicidal activity when used in combination was essentially equal to or less than that that of miconazole nitrate alone. From the results for the FIC Index of primary screening, it can be presumed that salicylic acid has a bacteriostatic combined use effect.

The results for benzalkonium chloride are shown in Figure 4. With benzalkonium chloride alone, fungicidal activity equal to that of miconazole nitrate was found against T. rub. and greater than that of miconazole nitrate was found against T. menta. On combined use, findings were below the detection limits for both fungi on the first day.

The results for decalinium chloride are shown in Figure 5

The fungicidal activity of decalinium chloride alone was equal to that of miconazole nitrate alone. On combined use, the findings were below the detection limit on the second day.

Evaluation of synergic effect on fungicidal activity was performed on the basis of the literature (Antimicrobial Agents and Chemotherapy, Feb. 1977, p. 225-228). Because an evaluation of efficacy was made when the difference in the number of surviving spores between use alone and combined use was greater than an order of 2, it was concluded that there was a synergic fungicidal effect between benzalkonium chloride and decalinium chloride.

Experimental Example 4

(1 Test microbial strains

Candida albicans

Staphylococcus aureus

(2) Method of preparation of microbial solutions

C. albicans was cultured for 24 hours at 28°C in Sabouraud agar culture medium (Eiken) and the organisms were suspended in sterilized physiological saline solution to approximately 10^6 organisms/ml, with the suspension being used as the microbial solution. S. aureus was cultured for 18 hours at 37°C in Mueller-Hinton culture medium (Eiken) and the organisms were suspended in sterilized physiological saline solution to approxiomately 10^6 organisms/ml, with the suspension being used as the microbial solution.

(3) Preparation of test drug preparations

The test drug preparations were prepared using miconazole nitrate and decalinium chloride. DMSO was used as the solvent for dissolution and dilution and a double dilution series in accordance with the test concentrations was prepared.

(4) Experimental method

The diluted test drug preparations were mixed with Sabouraud agar culture medium (Eiken) in a proportion of 1 : 99 and solidified, after which a solution of S. aureus was inoculated. It was cultured at 30°C for 2 days and the presence or absence of growth of bacteria was confirmed.

The diluted test drug preparations were mixed with Mueller-Hinton agar culture medium (Eiken) in a proportion of 1 : 99 and solidified, after which a solution of S. aureus was inoculated. It was cultured at 30°C for 24 hours and the presence or absence of growth of bacteria was confirmed.

(5) Evaluation and calculation equation
Calculation and evaluation were performed in the same way as in Experimental Example 1

(6) Results

The results are shown in Table 5

Table 5

Test microbial strain	FIC index
C. albicans	0.11
S. aureus	0.75

Synergic effects due to compounding of miconazole nitrate and decalinium chloride were confirmed against Candida albicans and Staphylococcus aureus.

Experimental Example 5

Figure 6 shows the results of a study in which tests similar to those in Experimental Example 3 were performed on the effect of the compounding ratio (1:0.12 ~ 1.00) when miconazole nitrate and decalinium chloride were used in combination.

As a result, at compounding ratios of 1:0.12 and higher during combined use, microbicidal activity was stronger than when miconazole nitrate and decalinium chloride were used alone, with a synergic effect also being found.

Experimental Example 6. Effect of lecithin

Lecithin, which is used as a base material for glyme is known as a deactivating agent of microbicidal agents such as quaternary ammonium salts (Chuichi Ishizeki, et al., Eisei Shikenjo Hokoku [Bulletin of the National Institute of Hygienic Sciences], No. 91 (1973)], for which reason a study was conducted of its effects on the synergic effect of miconazole nitrate and decalinium chloride.

Experiments like those in Experimental Example 3 were performed on lecithin for miconazole nitrate alone, the case in which they were combined at a compounding ratio (miconazole nitrate : lecithin = 1:0.5) and the cases in which decalinium chloride was used alone and when it was used in combination with miconazole nitrate, with the lecithin concentration set at 1.57 μg/ml.

No effects whatsoever were found at these lecithin concentrations.

<u>Optimum Mode for Executing the Invention</u>

We shall now describe this invention in specific terms by presenting examples.

Example 1

(Example of glyme formulation)

Miconazole nitrate	
Lidocaine	
Decalinium chloride	
Polyoxyethylene sorbitan monostearate	
Sorbitan monostearate	
1,3-Butylene glycol	1500 g
Neutral chain fatty acid triglyceride	1500 g
Glycerol monostearate	250 g
EDTA-2Na	[illegible] g
Purified water	total of 10,000 g

(Method of manufacture)

The oleaginous phase components (miconazole nitrate, lidocaine, sorbitan monostearate, neutral chain fatty acid triglyceride, glycerol monostearate and polyoxyethylene sorbitan monostearate) were added to the aqueous phase components (1,3-butylene glycol, EDTA-2Na, decalinium chloride and purified water) and the mixture was heated, after which 10,000 g of glyme was manufactured using known procedures.

Example 2

(Example of liquid preparation formulation)

Miconazole nitrate	
Decalinium chloride	
Dipotassium glycyrrhizinate	
BHT	
Ethanol	5000 g
Purified water	total of 10,000 ml

(Method of manufacture)

(Method of manufacture)

The drug preparation was dissolved in ethanol, after which purified water was added to make a total volume of 10,000 ml.

Example 3

(Example of gel cream formulation)

Miconazole nitrate	
Decalinium chloride	
Lidocaine	
Polyoxyethylene sorbitan monostearate	
Propylene glycol	1000 g
Liquid paraffin	500 g
Stearyl alcohol	
Carboxyvinyl polymer	
Diisopropanolamine	100 g
Purified water	total of 10,000 g

(Method of manufacture)

The oleaginous phase components (miconazole nitrate, lidocaine, decalinium chloride, polyoxyethylene sorbitan monostearate, liquid paraffin and stearyl alcohol) were heated and dissolved and then cooled to room temperature. Next, the carboxyvinyl polymer was dissolved in the water and propylene glycol and the solution was allowed to stand at room temperature, with the carboxyvinyl polymer being caused to swell. The aforementioned oleaginous phase and aqueous phase were stirred at room temperature, with a gel cream being manufactured.

Example 4

(Aerosol preparation formulation)

Raw solution:	Miconazole nitrate	
	Decalinium chloride	
	Dipotassium glycyrrhizinate	
	Ethanol	2500 g

Purified water 5000 ml

Spray agent: LPG 5000 ml

(Method of manufacture)

A container was filled with the raw solution, which was comprised of the principal drug components dissolved in the base agent of ethanol and purified water, after which a valve was installed and the vessel was filled with the spray agent, with an aerosol being made.

Brief Explanation of the Figures

Figure 1 shows the microbicidal activity of miconazole nitrate against T. rubrum (A) and T. mentagrophytes (B). The horizontal axis shows the number of days of storage and the vertical axis shows the logarithm of the number of surviving microorganisms/ml. (Specifically, 1 indicates 10^1 microorganisms/ml, 2 indicates 10^2 microorganisms/ml, 3 indicates 10^3 microorganisms/ml and 4 indicates 10^4 microorganisms/ml.)

Figure 2 shows the microbicidal activity of the combined use of various drug preparations against T. rubrum (A) and T. mentagrophytes (B). The horizontal axis shows the number of days of storage and the vertical axis shows the logarithm of the number of surviving microorganisms/ml.

MCZ indicates miconazole nitrate, BAC indicates benzalkonium chloride and DQ indicates decalinium chloride.

Figure 3 shows the microbicidal activity against T. rubrum (A) and T. mentagrophytes (B) when salicylic acid was used in combination. The horizontal axis shows the number of days of storage and the vertical axis shows the logarithm of the number of surviving microorganisms/ml.

MCZ indicates miconazole nitrate.

Figure 4 shows the microbicidal activity against T. rubrum (A) and T. mentagrophytes (B) when benzalkonium chloride was used in combination. The horizontal axis shows the number of days of storage and the vertical axis shows the logarithm of the number of surviving microorganisms/ml.

MCZ indicates miconazole nitrate and BAC indicates benzalkonium chloride.

Figure 5 shows the microbicidal activity against T. rubrum (A) and T. mentagrophytes (B) when decalinium chloride was used in combination. The horizontal axis shows the number of days of storage and the vertical axis shows the logarithm of the number of surviving microorganisms/ml.

MCZ indicates miconazole nitrate and DQ indicates decalinium chloride.

Figure 6 shows the results of a study of the effects of the compounding ratios when miconazole nitrate and decalinium chloride were used in combination. The horizontal axis shows the number of days of storage and the vertical axis shows the logarithm of the number of surviving microorganisms/ml.

MCZ indicates miconazole nitrate.

CLAIMS

1. A composition for antifungal agents characterized in that an imidazole antifungal agent and a quaternary ammonium salt are compounded.

2. A composition for antifungal agents characterized in that (A) miconazole, econazole, clotrimazole or bifonazole and (B) a quaternary ammonium salt are compounded.

3. A composition for antifungal agents characterized in that (A) miconazole, econazole, clotrimazole or bifonazole and (B) benzethonium chloride, benzalkonium chloride or decalinium chloride are compounded.

4. A composition for antifungal agents characterized in that an imidazole antifungal agent and decalinium chloride are compounded.

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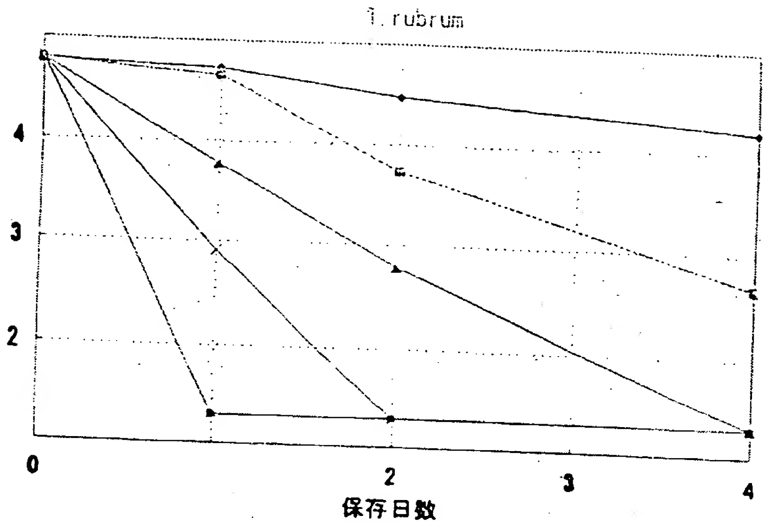

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[horizontal axis]: Number of days of storage

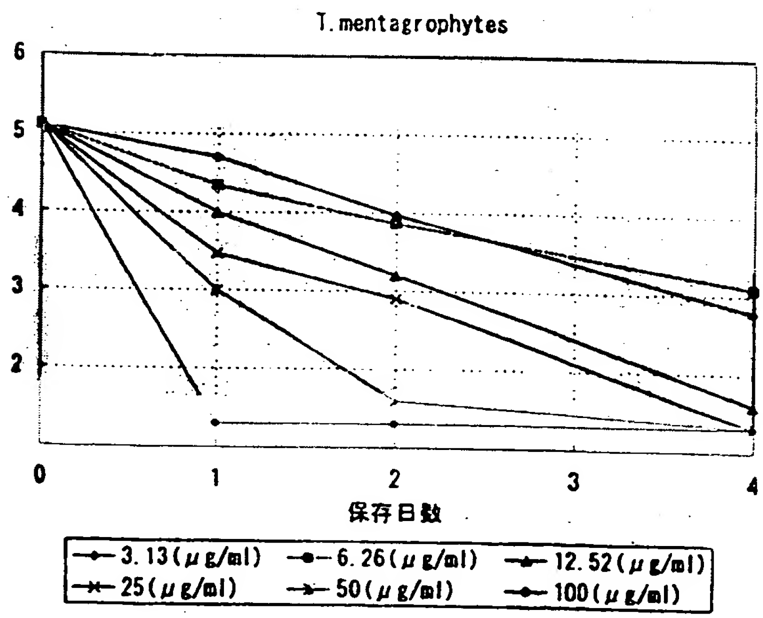

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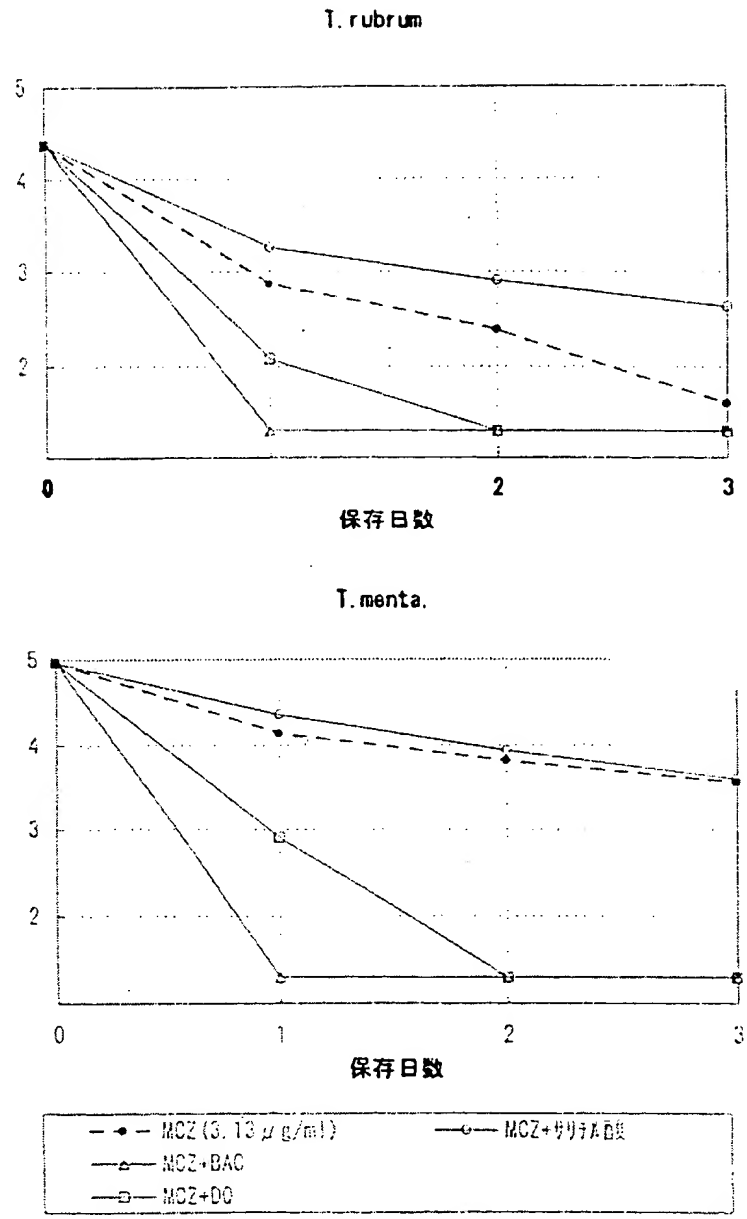
Figure 2
(A)

(B)



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[horizontal axis]: Number of days of storage

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[vertical axis]: Logarithm of number of surviving microorganisms
[horizontal axis]: Number of days of storage

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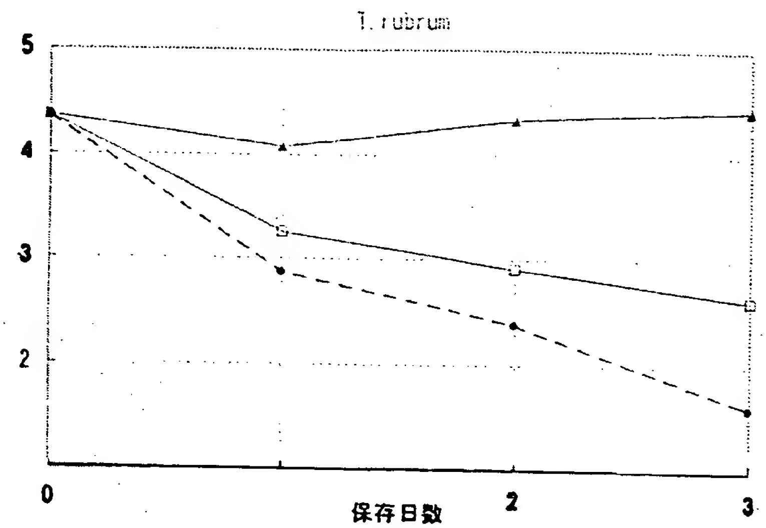
Figure 3

(A)



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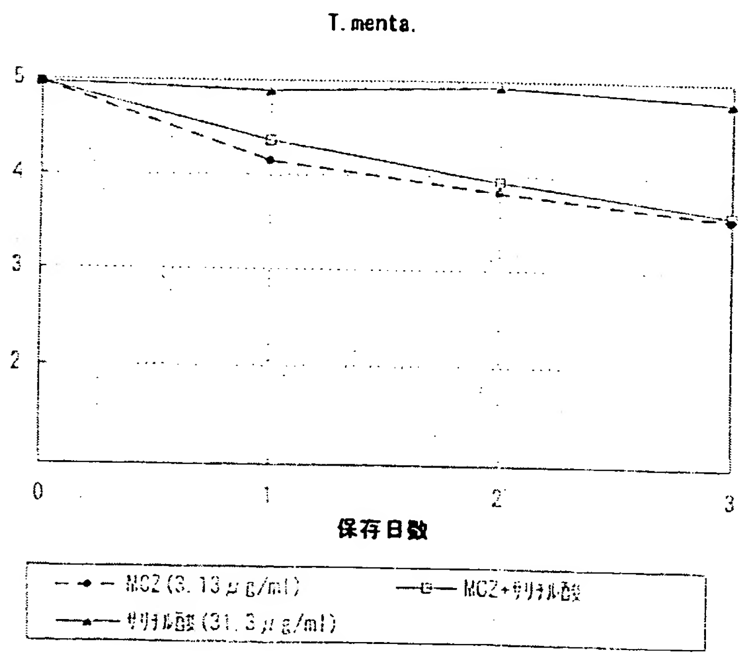

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[horizontal axis]: Number of days of storage

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[horizontal axis]: Number of days of storage

[in box at bottom of page, right side]: MCZ + salicylic acid

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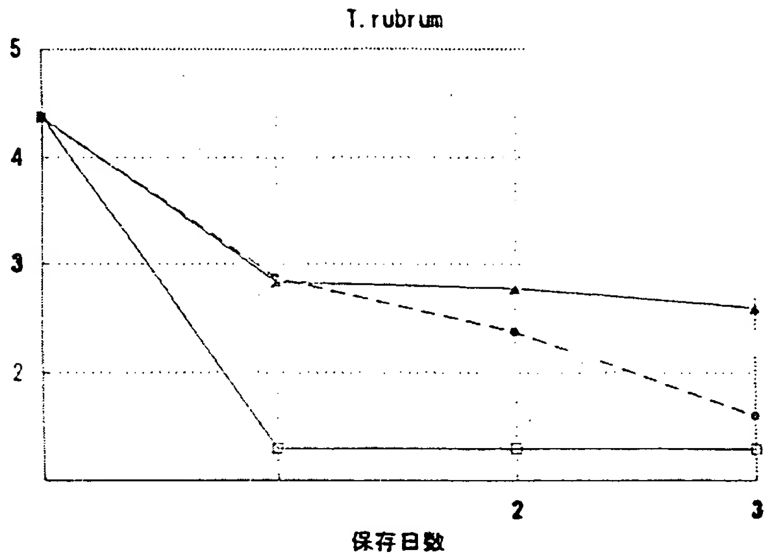
Figure 4

(A)



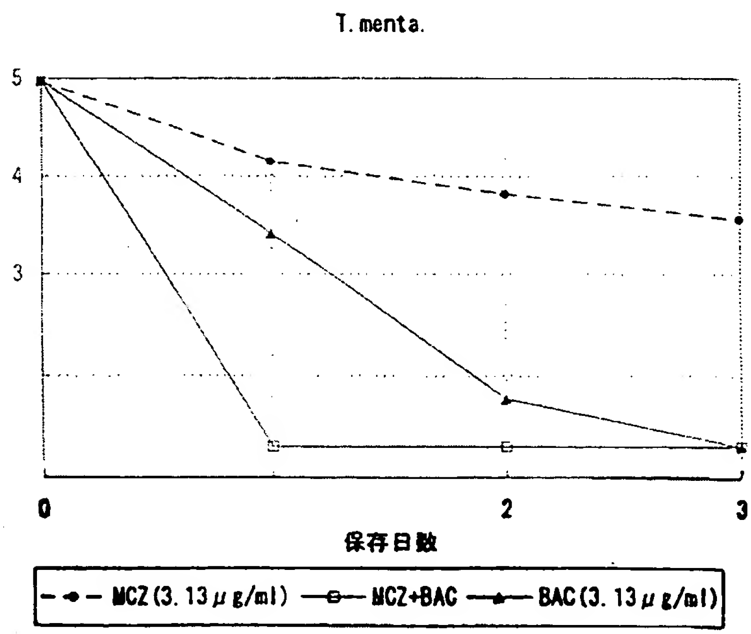


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Figure 5

(A)

(B)

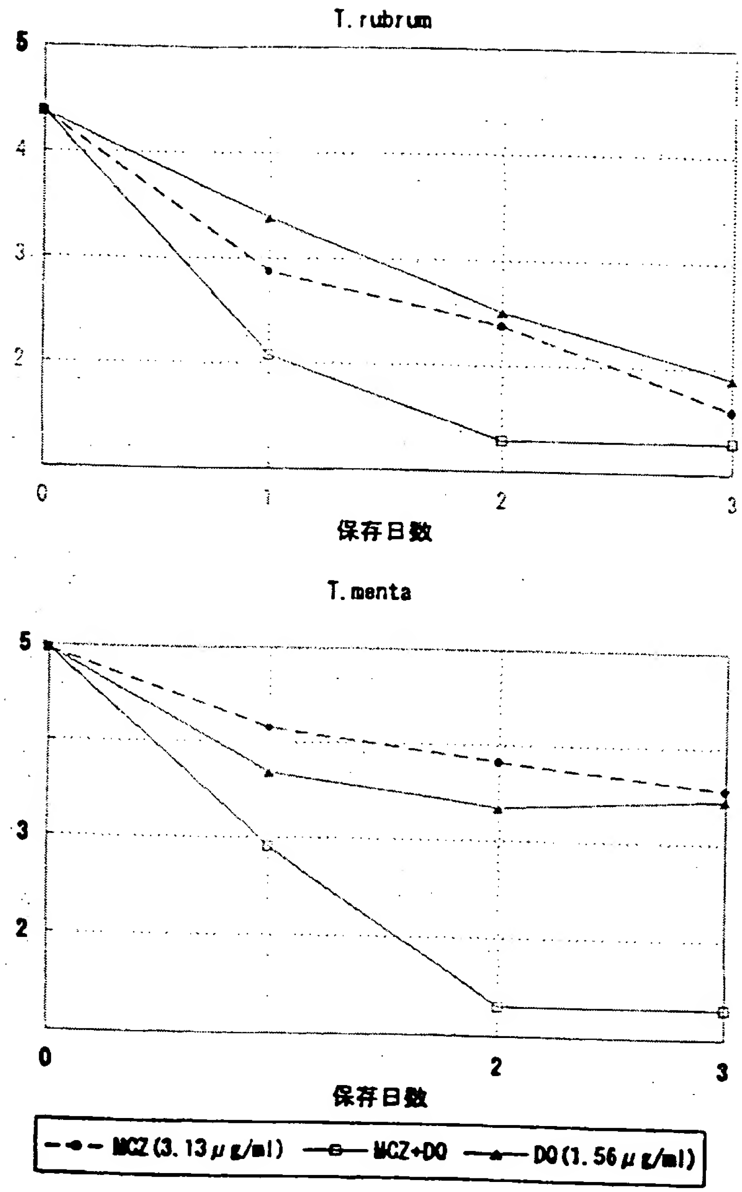

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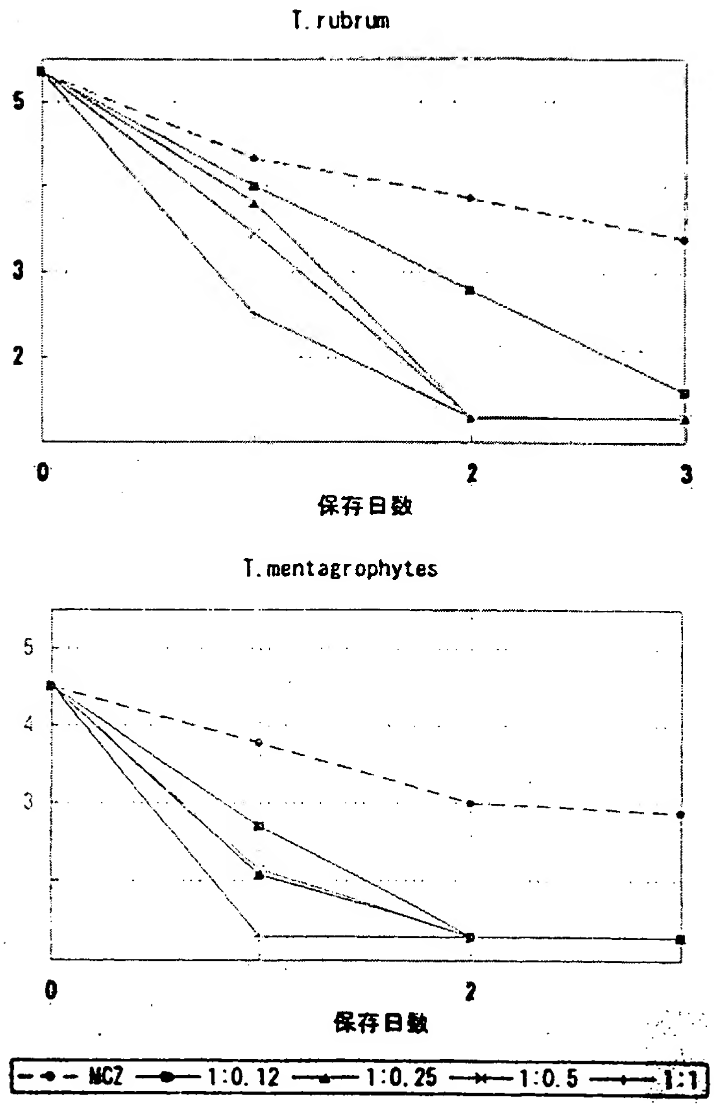
Figure 6

A)



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[vertical axis]: Logarithm of number of surviving microorganisms
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP96/01553

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl^6 A61K31/415, A61K31/14, A61K31/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int. Cl^6 A61K31/415, A61K31/14, A61K31/47

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP, 64-66121, A (CIBA-Geigy AG.), March 13, 1989 (13. 03. 89), Claim; page 4, upper left column, line 20 to lower left column, line 6 & GB, 2208598, A	1 - 4
Y	By the Pharmacist Society of Osaka Hospital "Drug Handbook (5th edit.)", Yakugyo Jihosha, February 2, 1995 (05. 02. 95), p. 1122-1125, 1266-1267	1 - 4

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"&" document member of the same patent family

Date of the actual completion of the international search August 28, 1996 (28. 08. 96)	Date of mailing of the international search report September 10, 1996 (10. 09. 96)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.